INTERNAL ROTATION IN AMIDES STUDIED BY PROTON MAGNETIC RESONANCE SPECTROSCOPY

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The following consists of a brief discussion of papers 1 through 6; additionally, solvent and substituent effects on barrier to torsions about the N-CO bond in amides will be discussed.

1 Drakenberg, T. and Forsén, S., "The Barrier to Internal Rotation in Amides. I. Formamide." J. Phys. Chem. 74, 1 (1970)

2 Drakenberg, T., Dahlqvist, K-I and Forsén, S., "The Barrier to Internal Rotation in Amides. II. N,N-Dimethyltrichloroacetamide." Acta Chem. Scand. 24, 694 (1970)

3 Drakenberg, T., Dahlqvist, K-I and Forsén, S., "The Barrier to Internal Rotation in Amides. IV. N,N-Dimethylamides. Substituent and Solvent Effects." J. Phys. Chem. (In Press)

4 Drakenberg, T. and Forsén, S., "The Barrier to Internal Rotation in Monosubstituted Amides.", Chem. Commun., 1971, 1404

5 Drakenberg, T., "The Barrier to Internal Rotation in Amides. VI. Acetamide. Solvent Dependent Entropy of Activation." (To be Published)

6 Olofsson, G., Stilbs, P., Drakenberg, T. and Forsén, S., "Concerted Conformation Exchange in Molecular Adducts of Antimony Pentachloride and N,N-Alkylureas." Tetrahedron, 91, 4583 (1971)

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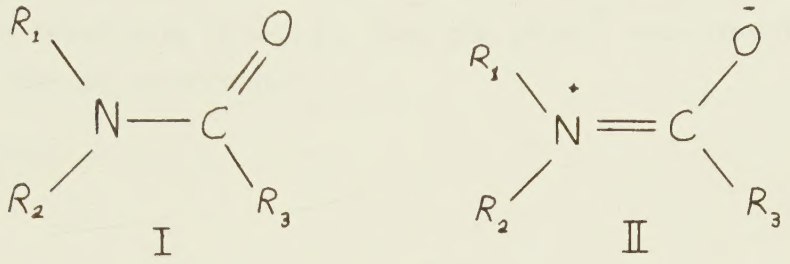
INTRODUCTION

Amides, the simplest model peptide, have long been extensively studied to obtain information about the barrier to internal rotation around the central bond. Pauling[1] originally postulated that the electronic structure of amides may be depicted as a linear combination of the resonance structures, I and II;



at the same time the resonance energy of the peptide bond was estimated by Pauling to be ca. 21 kcal/mol.

The first experimental evidence in support of a high barrier to internal rotation was adduced independently by Philips[2] and by Gutowsky et al.[3]. From the room temperature PMR spectrum of dimethylformamide (DMF) Philips calculated a lower limit for the interconversion rate constant of 38 sec^{-1}; Gutowsky obtained values for the free energy of activation for torsion about the N-C(O) bond for DMF and dimethylacetamide (DMA) to be ca. 22 and 19 kcal/mol, respectively.

From a biological viewpoint, however, secondary amides are of greater interest than tertiary amides. Thus, of interest are the barriers to internal rotation in N-methylformamide (NMF) and N-methylacetamide (NMA). These have been estimated from i.r. data as being 14 kcal/mol[4], and 28 kcal/mol for NMF[5]. In a recent NMR study of NMF, Neuman et al.[6] report free energy of activation values for the two isomers as being 22. and 20. kcal/mol (neat).

Attempts using differing quantum mechanical methods have also

been made to calculate the barrier to internal rotation in amides. Christiansen et al.[7] have recently published an ab initio calculation of the barrier to internal rotation in formamide, which gives ΔE=19.4 kcal/mol. This value can, however, not be directly compared with experimental values, as the calculations "refer" to gas phase while the experimental values, to date, refer to solution phase. It does, however, seem reasonable to assume that gas phase[8] measurements will shortly be performed.

RATE PARAMETERS FROM NMR SPECTRA

PMR spectroscopy has been used for studying kinetic processes for nearly 20 years and has shown to be a very useful tool for the evaluation of barriers hindering various internal motions, e.g. pyramidal and linear inversions, ring reversals, or internal rotation[9]. The possibility of using this method to obtain interconversion rates was first pointed out by Hahn and Maxwell[10], and later by Gutowsky et al.[11] They showed that it was possible to modify the Bloch equation (1) to take chemical exchange into account.

$$\frac{dG}{dt} + \left(\frac{1}{T_2} - i(\omega_o - \omega)\right) \cdot G = -i\gamma H_1 M_o \qquad (1)$$

According to the procedure of McConnel[12], this derivation is as follows. The Bloch equations for two sites, A and B, are given by

$$\frac{dG_A}{dt} + \left(\frac{1}{T_{2A}} - i(\omega_o - \omega_A)\right) \cdot G_A = -i\gamma H_1 M_{OA} \qquad (2)$$

and

$$\frac{dG_B}{dt} + \left(\frac{1}{T_{2B}} - i(\omega_o - \omega_B)\right) \cdot G_B = -i\gamma H_1 M_{OB} \qquad (3)$$

These can be modified for chemical exchange by insertion of exchange terms $\tau_B^{-1} \cdot G_B$ and $\tau_A^{-1} \cdot G_A$, where τ_A and τ_B are the pre-exchange lifetimes at each site.

Thus,

$$\frac{dG_A}{dt} + \alpha_A \cdot G_A = -i\gamma H_1 M_{OA} + \tau_B^{-1} \cdot G_B - \tau_A^{-1} \cdot G_A \qquad (4)$$

and

$$\frac{dG_B}{dt} + \alpha_B \cdot G_B = -i\gamma H_1 M_{0B} + \tau_A^{-1} \cdot G_A - \tau_B^{-1} \cdot G_B \qquad (5)$$

where,

$$\alpha_A = \left(\frac{1}{T_{2A}} - i(\omega_o - \omega_A)\right) \quad \text{and}$$

$$\alpha_B = \left(\frac{1}{T_{2B}} - i(\omega_o - \omega_B)\right)$$

Eqs. (4) and (5) can be solved for the slow passage ($dG_A/dt = dG_B/dt = 0$) case: the solution is

$$G = G_A + G_B = -i\gamma H_1 M_0 \frac{\tau_A + \tau_B + \tau_A \cdot \tau_B(\alpha_A p_A + \alpha_B p_B)}{(1 + \alpha_A\tau_A)(1 + \alpha_B\tau_B) - 1} \qquad (6)$$

noting that,

$$M_{0A} = p_A M_0$$

$$M_{0B} = p_B M_{0B}$$

In the slow exchange limit this results two lines, one centered at ω_A, the other at ω_B, in the fast exchange limit only a single line centered at $(\omega_A \cdot p_A + \omega_B \cdot p_B)$. Eq. (6) can under special assumptions, be simplified so that the spectral shape is described by a single parameter; e.g., the half width of the signal, or the peak-to-peak separation (see paper 2). Before fast digital computers were commonly available it was necessary to use these approximate formulas, as it is extremely time consuming to hand calculate the total line shape from eq. (6). Values obtained from the approximate formulas are, however, not very reliable, as can readily be exemplified by N,N-dimethylformamide, whose Arrhenius energy of activation determined by sundry

approximate methods varies between 7 and 27 kcal/mol[13]. Due to this and other similar examples, the reliability of the line shape method in the determination of activation energies has been questioned. It has, however, been shown that when total line shape methods are used, without any simplifying assumptions, the activation parameters obtained by different authors coincide very well[14-17] (paper 3). In a few cases it has also been possible to evaluate the activation parameters from both total line shape method and equilibration technique, and these show good agreement[18-20, 41, 59].

Allerhand and Gutowsky[21] have discussed the errors involved in the use of the approximate formulae, and shown that one must be very careful in using them. This is discussed in paper 2, where it is also shown that small systematic errors in the transverse relaxation time, T_2, or the chemical shift difference, $\delta\nu$, can cause errors in the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ which are much higher than the random errors, whereas $\Delta G^{\neq}_{Tc}$ is nearly uneffected by these factors. Eq. (6) is valid for an uncoupled two site case. This means an A_nM_m spectrum, without spin coupling between A and M, which goes to an A_{n+m} spectrum. When these nuclei are coupled, with a first order coupling, to a third nucleus (or group of equivalent nuclei, x_i) this can be taken into account by summing up a pertinent number of independent AM spectra; for example, for DMF, the N-methyl protons are coupled to the formyl proton, and there are thus two A_3M_3 spectra with different $\Delta\nu_{AB's}$, the result of the non-equivalence of the two coupling constants. When the coupling constants are small, as for DMA, 0.5 and 0.2 Hz, fine structure is resolvable only at very high or very low exchange rates. One can than be lead to approximate the extra broadening due to the coupling as a T_2 broadening. However, this is unsatisfactory. We have analysed the line shape for neat DMA to obtain the rate constants, both by summing four independent A_3M_3 spectra with intensities 1:3:3:1, as well as by changing the T_2-values to account for the extra

broadening[22]. The obtained value for E_a and $\Delta H^{\neq}$ are ca. 2.5 kcal/mol too high when the couplings are not taken into account.

For more complicated exchanges like scheme (7)

(7)

it is possible to use the McConnell method to modify the four Bloch equations to take account of the exchange, and obtain the complete line shape equation. This has been used in paper 4. There is no theoretical problem in extending this to even more complicated problems.

When the exchanging nuclei are coupled to each other the spectra become more complex and a density matrix formalism[23, 24] becomes convenient to obtain the theoretical line shapes. Alexander[24] has however shown that it is possible to obtain an explicit expression for an AB case, where A is coupled to B and exchanges with B. Also, for the AB case, it is possible to sum up several independent spectra to take account of couplings to other nuclei. It is also possible to derive line shape equations for exchanges like scheme (7).

For more complex spectra, for example ABC → A_2C, it is necessary to use the density matrix formalism. Computer programs are available for such problems[9, 25, 26] and the program due to Binsch[9] being the most general; but even with the Binsch program it is not possible to handle exchange schemes like (7).

The fitting of the parameters used in the total line shape equation can be performed in two slightly different ways; either a total computer-made fitting procedure, in which the computer compares the theoretical and the digitized experimental spectra

point by point, or a visual fitting of plotted theoretical spectra to the experimental ones, can be made. The computerized fitting has been described in paper 2 and also used for obtaining the activation parameters reported in paper 3. Similar fitting procedures have previously been described[27-29]. The digitizing was first made by hand, (paper 2) but during the course of this work (paper 3) a devise for automatic digitizing of the spectra was made. This consists of a home-made analog digital convertor (ADC) and an Addo paper tape punch. The ADC is trigged directly from the step motor in the recorder of the NMR spectrometer. This method has also been used to evaluate the rotation rates in acetamide (an ABX_3 going to an A_2X_3 spectrum (paper 5)).

In order to minimize the mean square sum calculated by the computer, several hundred calculations of the spectrum are usually necessary: such a procedure is quite time consuming. For systems where the density matrix program has to be used, the use of such a computerized fitting is not realistic; for example, using the DENSMAT program, it would take ca. one hour of computer time (Univac 1108) to evaluate the parameters for an ABCD spectrum consisting of two hundred points. For formamide (paper 1), which is an ABCX system at low temperature and an A_2BX at high temperature, the evaluation of the rate constants were made by means of a visual comparison of theoretical to experimental spectra. This method was likewise used for N-methylformamide (NMF) and N-methylacetamide (NMA) (paper 4). The accuracy in the visual fitting procedure is most likely not quite as good as in the computerized fitting. Another drawback is that it is not a completely objective method. For both fitting procedures it is necessary to have high quality, non-distorted spectra.

ROTATIONAL BARRIERS IN AMIDES

SOLVENT EFFECTS

The barrier to internal rotation in amides has, in several papers[30-32], been shown to be solvent dependent; however, few systematic and reliable investigations of these solvent effects have been made. I will here discuss the effects of non-polar aprotic, dipolar aprotic and protic solvents separately, and, additionally, specific solute-solute interactions.

a) Non-polar aprotic solvents

Rabinovitz and Pines[33] have studied the chemical shift difference, $\Delta\nu_{AB}$, between the two dimethylamino PMR signals of DMF in CCl_4 solution as a function of amide concentration and temperature. They found that $\Delta\nu_{AB}$ decreases with increasing dilution and temperature. This was interpreted as being caused by an amide monomer-dimer equilibrium; assuming that the monomer and dimer chemical shift differences were independent of concentration and temperature, it was possible to calculate the enthalphy of association as being ca. -6 kcal/mol and the entropy of association as -15 cal/mol K. Thus, there is a strong amide-amide interaction and the torsional barrier will thus change with concentration, if the barrier height is not the same for both monomer and dimer. As might be expected, the barrier height increases with increasing amide concentration, showing that the monomer barrier is lower than the dimer barrier. Calzolari et al.[30] have performed a similar study for DMF and DMA dissolved in a variety of solvents, and found a similar variation of the chemical shift difference. They have also given activation parameters for the hindered internal rotation; these data are, however, not given with sufficient accuracy, and additionally, these values do not seem to be very reliable, because of the use of approximate (one-parameter formulas) for evaluating the rate constants. Assuming a low and constant entropy of activation, some information of the solvent

effect could be obtained from the knowledge of the coalescence temperature, T_c, and the chemical shift difference at coalescence. Their temperature measurements, however, do not seem to be reliable as they have found a T_c of 386 K[14] for neat DMF, some 5-6° lower than that found in some recent works (paper 3). Their T_c values for DMF and DMA indicate, however, that the barrier for both amides are lower in pentachloroethane than in 1,1,2,2-tetrachloroethane at the same amide concentration. Whittaker and Siegel[34] have found similar variation for DMF dissolved in hexamethyl-disiloxane (HMDS) and $CFCl_3$, with the first coalescence temperature lower. We have shown in paper 3 that the DMF torsional barrier is lower in decalin than in tetrachloroethene solution. These observations indicate that there might be effects other than the monomer-dimer equilibrium, which determines the barrier height in non-polar solvents, since there is no reason to assume that DMF is more dissociated to monomers in decalin than in tetrachloroethene or in HMDS than in CCl_3F. Thus we have to assume that these solvents will effect the monomer and/or dimer rotational barriers. This might be understood as being caused by a stabilization of the more polar ground state of the amide in more polar solvents; there is, however, no sufficiently reliable data available to verify this assumption. This effect, however, is presumably small compared to the difference between the monomer and dimer barriers, which seems to be of the order of 1 kcal/mol.

The entropy of activation for rotation in tertiary amides is always (except ref. 32) found to be small (< 5 cal/mol K) when total line shape methods have been used to evaluate the rate constants. We believe that reported data with $\Delta S^{\neq}$ values not within this range are incorrect.

b) Polar aprotic solvents

Solvents included in this group, as defined by Parker[35], which have been used as solvents in studies of the torsional barriers

in amides are ketones, tertiary amides and DMSO. I will first discuss the effect of these solvents on the barrier height in tertiary amides, and than in primary and secondary amides, which possess protons that can hydrogen bond to these solvents.

Both ketones and DMSO have dipoles similar to those in amides and might therefore substitute one amide molecule in the amide dimers, without affecting the other amide molecule seriously. Neuman *et al.*[15] have found that the DMA-d_3 barrier height is increased by *ca.* 0.3 kcal/mol when the amide is dissolved in DMSO, compared to the neat amide, and we have found (paper 3) that the barrier, in some N,N-dimethylalkylamides, is slightly lower when the amide is dissolved in acetone-d_6 compared to neat amide (not more than 0.2 kcal/mol). These observations indicate that the DMSO-amide interaction is stronger and the acetone-amide weaker than the amide-amide interaction. Calzolari *et al.*[30] have, from their study of the variation of the dimethylamino chemical shift differences with amide concentration and temperature, in DMF and DMA, concluded that both ketones and ethers associate with tertiary amides in the same way as the amide itself. They have also found that the DMF coalescence temperature does not vary significantly with amide concentration for cyclohexanone solutions; kinetic data for ether solutions are, however, not given. The variation of the chemical shift difference between the dimethylamino signals, for DMF in ethers (tetrahydrofuran and diethylether) given by Calzolari *et al.*[30] deviates markedly from those of ketones (acetone and cyclohexanone) and ethylacetate, and it can, therefore not be determined if the effect from ethers on the torsional barrier is similar to the polar or non-polar aprotic solvents, before kinetic data for the hindered rotation in amides dissolved in ethers, become available.

In primary and secondary amides the association between the amide molecules is the result of hydrogen bonding between >N-H and >C=O

moieties and is found to be quite strong[36]; even in 10 mol% solutions, in non-polar solvents, these amides are, almost exclusively, present as dimers. In contrast to the large amount of data published on rotational barriers in N,N-dialkylamides, very little has been made on primary and secondary amides[6,37-39]; the only kinetic data obtained via total line shape methods are those given in papers 1, 4 and 5 and ref. 6.

For N,N-dimethylamides, in every solvent, the entropy of activation found from total line shape methods, is always close to zero and mostly slightly negative (except ref. 32); for formamide in methylpropylketone or diglyme (paper 1) and acetamide in acetone or DMF (paper 5) and NMF neat or in formamide[6] the entropy of activation is definitely positive, ranging from +2.7 for formamide in methylpropylketone to ca. 9 cal/mol·K for acetamide in DMF or NMF in formamide. This can be understood as being caused by the hydrogen bonding between amide and solvent being broken during the amide internal rotation (see also next section).

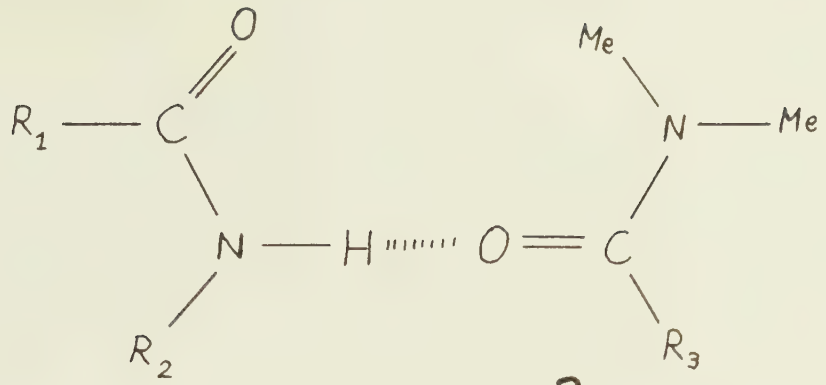
The strength of the hydrogen bond can probably be correlated to the donicity or donor number (DN) as defined by Gutmann[40]. The DNs for acetone, diethylether and DMF are 17.0, 19.2 and 26.6, respectively, in good agreement with the entropies of activation value found for formamide, acetamide and NMF. There is no significant difference between the $\Delta S^{\neq}$ values found for ether or ketone solutions but in DMF, formamide or NMF solutions $\Delta S^{\neq}$ is considerably higher.

c) Protic solvents

For amides dissolved in protic solvents (e.g. water[17] and formamide[31]) the torsional barrier is found to be higher than for other solutions. This observation can be interpreted as being caused by a hydrogen bonding between the solvent and amide carbonyl oxygen which may increase the double bond character of

the N-C(O) bond. The fact that the spin coupling constant between the methylaminoprotons and the C-methyl protons in DMA is higher in water than in acetone solution ($J_{\underline{cis}}$ = 0.4 and 0.1 Hz, resp., and $J_{\underline{trans}}$ = 1.1 and 0.5 Hz, resp., paper 3) indicates also that the N-C(O) double bond character increases with hydrogen bonding.

In accordance with the rather high positive entropy of activation found for primary and secondary amides in dipolar aprotic solvents, one should expect to obtain similar values for tertiary amides dissolved in protic solvents; this has, however, to date, not been observed[17,31,41]. Siddall *et al.*[41] have studied the effect of phenol-amide association on the amide torsional barrier, and found that the barrier height ($\Delta G^{\neq}$) increases with phenol concentration; the entropy of activation is, however, never significantly different from zero. They propose that this is the result of the amide-phenol interaction being extended over domains larger than amide-phenol pairs, and that an amide internal rotation and simultaneous rupture of a hydrogen bond will not drastically affect the order in the extended interaction domain. There is therefore no reason to expect a large entropy of activation for the hindered internal rotation. Using the same argument, however, there should be no reason to expect a large positive entropy of activation for the torsional barrier for DMF dissolved in formamide or for acetamide dissolved in DMF. In these latter two solutions, the solvent solute interaction is very similar. For DMF in formamide the entropy of activation is found to be about zero, but for acetamide it is found to be *ca.* 9 cal/mol K. This dissimilarity can most easily be explained by assuming that the hydrogen bond is broken when the internal rotation takes place in molecule 1 but not when it occurs in molecule 2. For neat NMF and for NMF dissolved in formamide both types of hydrogen bonds can be present, simultaneously, in the observed amide, but as high positive entropies of activation have never been observed for tertiary amides



1. 2.

dissolved in protic solvents, we believe that the high $\Delta S^{\neq}$ values for NMF in formamide is caused by rupture of the NMA N-H formamide C=O hydrogen bond.

d) Specific solute-solute interaction

Temussi et al.[17] have found that the torsional barrier in DMA (aq) decreases when $AgNO_3$ is added. A similar decrease in the barrier to internal rotation has also been found for DMF in acidic aqueous solutions[32,42,43]. Intuitively one should expect that the barrier should increase with increasing Ag^+ or H^+ concentration, due to the interaction between the positively charged ions and the carbonyl oxygen. To explain the found change in the torsional barrier it is necessary to assume that there is an interaction between the positively charged ion and the nitrogen or carbonyl carbon atom. As discussed by Temussi et al.[17], it is only necessary that the ion-nitrogen interaction is present in a small amount of the ion-amide pairs, to cause a decrease of the rotational barrier, because the barrier height in this compound should be very low.

Gore et al.[44] have shown, by NMR, that the addition of a Lewis acid to an amide solution increases the barrier dramatically. The quality of these measurements is not high, but the effect from the Lewis acid must be regarded as real. Similar effects have been observed for various alkylureas (paper 6). The barrier is 5-6 kcal/mol higher for the N,N'-dimethylurea - $SbCl_5$ complex than

for the free ureas[45,46]. In paper 6 it has been shown that the interconversion in the N-methyl-N'-ethylurea - $SbCl_5$ complex takes place in a concerted fashion. The same rotation rate constants were found for both the N-methyl and the N-ethyl groups, which would not be the case if these rotations were not coupled.

Matsubayashi and Tanaka[47] have studied the influence of several Lewis acids on the chemical shifts of the dimethylamino protons in p-substituted N,N-dimethylbenzamides. They have also found that the torsional barrier height ($\Delta G^{\neq}$) increases by about 4 kcal/mol on addition of an excess of tin tetrachloride. On the other hand they found that the barrier decreases on addition of germanium or silicon tetrachloride, showing that these, at least to some degree, are bound to nitrogen.

Substituent effects

Very many various amides and similar compounds have been studied by NMR spectroscopy, and total line shape methods are now often used (for a review see ref. 48). There is, however, to date, no thorough examination of the effect of different substituents on the torsional barrier in amides, available, but some conclusions can be drawn from a comparison of the published data; the solvent effect has, however, to be kept in mind. I will, in the following discuss the effect of N-substituents and C-substituents separately, and all effects will be in terms of changes in the free energy of activation.

N-substitution

The effect from these substituents can be separated into contributions from dipolar, electronic and steric interactions.

a) Dipolar effects

As discussed in paper 3 the dipolar attraction between the N-methyl group and the carbonyl oxygen in NMF and NMA will stabilize the s-trans relative to the s-cis conformer. In NMF the steric interactions are presumably quite similar in the two conformers and it is thus the dipolar attraction that is responsible for the s-cis to s-trans population ratio of 1:9[49], and the attraction is found to be ca. 1.5 kcal/mol stronger for a methyl syn to oxygen than for a methyl anti to oxygen.

The dipolar effect in NMA is probably similar to that in NMF, but as there is an additional steric interaction, this can not be verified. The same holds true for all N,N-dimethylamides. In formanilides[50,51] on the other hand, the population ratio is close to 1, showing that the dipolar interaction from a phenyl group is sufficiently different from that of a methyl group.

b) Electronic effects

Electron donating substituents are assumed to increase[76] and electron withdrawing substituents to decrease the torsional barrier. Thus an N-alkylsubstituent should cause an increase in barrier relative to the primary amide. This trend has been found on going from formamide to N-methylformamide and from acetamide to N-methylacetamide (papers 1, 4 and 5 and ref. 6). The values for NMF and NMA (paper 4) are, however, rather inaccurate, and, additionally, are not directly comparable with other amide values, due to the high concentrations employed. In the concentrated solutions, the amides are associated to a high degree[36] and the barrier height are therefore increased. The values given by Neuman et al.[6] refers to protic solvents, and are also thus not directly comparable. The magnitude of the effect of an N-methyl-substituent can not be stated accurately, but the electronic effect from a methyl group seems to be of the order of 1 kcal/mol

for both NMF and NMA. The insertion of a second methyl group on nitrogen has only a small effect. The DMF torsional barrier is found to be ca. 0.5 kcal/mol higher than the comparable NMF barrier (paper 4). The exchange of one of the methyl groups in DMF with $-CH_2C_6H_5$ [18] or $-CH_2CH_2Cl$ [52] has virtually no effect on the torsional barrier.

From the data given by Gehring et al.[52], free energy of activation values can be calculated for N-methyl-N-vinyl-acetamide and N-methyl-N-vinyl-formamide, which are 1.5 kcal/mol lower than the corresponding N,N-dimethylamide values. The vinyl group has reduced the double bond character in the amide N-C bond, by competitive conjugation with the nitrogen lone pair. A similar effect should be expected from the phenyl group in formanilides; the formanilide barrier[50] is found to be ca. 1 kcal/mol lower than the NMF barrier, and close to the formamide barrier.

The effect from competitive conjugation has also been observed for molecules where the nitrogen atom is included in a five membered ring. The torsional barrier in N-acetylpyrole[53,54] is ca. 6 kcal/mol lower than the 2-methyl-N-acetyl-pyrrolidin barrier[55]; this can partly be the result of a net steric repulsion in the ground state, which will be discussed below.

c) Steric and ring strain effects

The barrier to internal rotation decreases when the nitrogen substituent changes from methyl to ethyl or from n-propyl to i-propyl[56]; this is attributed to a larger steric repulsion between the nitrogen and carbon substituents in the ground state than in the transition state. The electronic effect from these slightly electron donating groups should change the barrier in the reverse order.

The effect of increasing volume of the N-substituent is also

reflected in the population ratio for different N-alkyl-formamides; 92 % of the trans conformer in N-methylformamide and 70-82 % in N-t-butylformamide[49,57], corresponding to a change in ΔG^{O} of 0.5-0.9 kcal/mol at 300 K. This change in the population ratios is the result of an increasing steric repulsion between oxygen and the nitrogen substituent, with increasing volume of this substituent.

A few amides, where the nitrogen atom is included in a ring have been studied[53-55,58-60]. For a saturated five membered ring the barrier height is approximately the same as for the comparable N,N-dimethylamide, but for a six membered ring it is ca. 2 kcal/mol lower. This observation can not be explained as arising from ring strain effects; perhaps the lowering is partly the result of a larger steric interaction between the α-carbon, equatorial protons and the acetyl group, than between the corresponding five membered ring protons and the acetyl group (c.f. ref. 61). When the nitrogen atom is included in a three membered ring, the torsional barrier is so low that it can not be obtained by means of PMR spectroscopy[67] (less than 6 kcal/mol). The strong ring strain effects in a three membered ring prohibit the nitrogen from assuming a planar conformation, the ground state for the rotational process. In these systems there is instead an observable barrier to nitrogen inversion[67].

C-substitution

The effect from C-substituents can, as for N-substituents, be divided into contributions from electronic and steric interactions.

a) Electronic effects

The difference in barrier between formamide and acetamide is almost exclusively due to electronic effects, because the steric

effect is presumably very small. Both hyperconjugation and the inductive effect from a methyl group tends to stabilize the transition state more than the ground state and the rotational barrier in acetamide is therefore lower than in formamide (ca. 1 kcal/mol, papers 1 and 5). These two amides are the only primary amides whose torsional barriers are known, and it is hence only for the methyl group that it is possible to separate the contributions from electronic and steric effects with an acceptable accuracy.

It has been shown that the barrier to internal rotation in N,N-dimethylbenzamide (DMB)[32,62-64] is ca. 1 kcal/mol lower than the DMiBu barrier (ca. 2.5 kcal/mol lower than the DMA barrier). It is not obvious which amide should be used to compare with DMB to obtain similar steric interactions. It is, however, clear that the barrier is lowered by the electronic effects, and this is easily explained by a larger decrease in the transition state energy than in the ground state energy due to conjugation; it has, however, been shown that the angle between the N-C$^{=O}$ plane and the benzene ring is 45°[65], showing that the steric interaction in the ground state is considerable. The ground state energy can therefore be increased due to this steric repulsion. Also for the substituents -CH=CH$_2$ ($\Delta G^{\neq}$=16.1 kcal/mol[62]), -CH==CH-C$_6$H$_5$ (16.3[66]), -CH=CH-CH$_3$ (14.3[66]) and -CH=CH-CH=CH-CH$_3$ (16.2[66]) the barrier is lower than for comparable alkylamides. In these compounds the steric repulsion is presumably much lower than in benzamide and probably comparable to that in DMA, and the electronic effect (conjugation) can therefore be estimated to lower the barrier with 2-4 kcal/mol.

For urea ($\Delta G^{\neq}$=14.3 kcal/mol[45]) an even more pronounced effect from competitive conjugation is observed, the effect, however, decreases drastically when one of the nitrogen atoms is included in a three membered ring[67]. The ring strain effect prohibites the nitrogen to be sp^2-hybridized.

Additionally the torsional barrier for carbamates is, due to conjugative effects, lower than for corresponding amides[29,68]; the inductive effect from oxygen should tend to increase the barrier height.

It has often been assumed that the cyclopropyl ring could take part in conjugation as efficiently as a double bond[69], and the barrier is also found to be the same for R = cyclopropyl as for R = -CH = CH_2, and additionally, the same value on the barrier height is found when R is aziridine[67].

The barrier height should increase with electron withdrawing capability of the substituent, Reeves and Shaw[72] have, however, found that the torsional barrier ($\Delta G^{\neq}$) in N,N-dimethyl carbamyl fluoride (DMCF) is only 18.1 kcal/mol; almost 3 kcal/mol lower than the DMF barrier. They have, however, from the small shift difference between the two N-methyl signals, assumed that the delocalization of fluorine 2pπ-electrons may be significant in the ground state. This delocalization could also be responsible for the low torsional barrier. This effect is even more pronounced for N,N-dimethyl carbamyl chloride (DMCC), whose barrier height is found to be only 16.3 kcal/mol[73]. Both DMCF and DMCC have been investigated in CCl_4-solution.

The only substituent for which it has been possible to detect any barrier increasing effect is -CF_3[62,70,71]. The most accurate value for N,N-dimethyltrifluoroacetamide (DMTFA) is 18.05 kcal/mol[71] (CCl_4-solution), which should be compared with the DMA barrier, 17.33 kcal/mol[71] (CCl_4-solution). The steric interactions in the ground state of DMTFA is stronger than in DMA, which will reduce the barrier height. The inductive effect from the -CF_3 group will therefore probably cause an increase in the barrier height of ca. 1 kcal/mol. In N,N-dimethyltrichloroacetamide the

steric repulsion in the ground state is so strong that the torsional barrier is ca. 3 kcal/mol lower than the DMA barrier (paper 2, ref. 62, 63, 74).

b) Steric interactions

The steric effect from a C-substituent will mostly tend to lower the barrier, because the steric repulsion is stronger in the ground state than in the transition state. The exception from this will be discussed later.

From the fact that the DMA barrier is 3 kcal/mol lower than the DMF barrier (paper 3) it can be concluded that the steric repulsion between an N-methyl and the C-methyl cis to each other is ca. 2 kcal/mol (the electronic effect is responsible for one kcal/mol, see above) and from the population ratios in NMA (1:100) and NMF (1:9) this effect is found to be 1.5 kcal/mol (paper 4). When the substituent changes from Me- to Et- or iso-Prop- the barrier decreases slightly, probably as a result of steric interactions; there can also be a small contribution from electronic effects. In N,N-dimethylpivaloyamide the torsional barrier is 5 kcal/mol lower than in N,N-dimethyl-iso-butyramide, and this must be due to the steric repulsion which will increase the initial state energy much more than the transition state energy.

In benzamides with bulky ortho substituents the rotational barrier height is unusually high, over 30 kcal/mol for N-methyl-N-benzyl-2,4,6-tri-t-butylbenzamide[75]. In this substance the ortho substituents prohibits the coplanarity between the phenyl ring and the N-C$^{=O}$ plane, which means that the barrier can not be lowered due to conjugation, and, additionally, in the transition state there will be a strong steric repulsion between the N-substituents and the ortho substituents causing an increased transition state energy.

Conclusions

In spite of the tremendous amount of data available on torsional barriers in amides, especially tertiary amides, it is often difficult to use these data to obtain accurate values on the effect on the barrier height from various substituents. Solvent effects can be of the same order of magnitude as the substituent effect and since a variety of solvents have been used, this can give rise to erroneous conclusions; additionally, a large portion of the available data has been evaluated by means of inaccurate methods, introducing uncertainties, sometimes larger than the observed effect.

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